Understanding and Enhancing Sepsis Survivorship: Priorities for Research and Practice

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ABSTRACT

An estimated 14.1 million patients survive sepsis hospitalization each year. Many survivors experience poor long-term outcomes, including new or exacerbated neuropsychological impairment, functional disability, and heightened vulnerability to further health deterioration, including recurrent infection, cardiovascular events, and acute renal failure. However, current guidelines and interventional trials have focused on shorter-term survival, so there is little data on how to best promote longer-term recovery. To address this unmet need, a Colloquium on “Understanding and Enhancing Sepsis Survivorship” was held in February 2018, sponsored by the International Sepsis Forum. The goals of the Colloquium were to identify (1) gaps and limitations of current research, (2) shorter-term research priorities, and (3) longer-term research priorities for understanding and enhancing sepsis survivorship, informed by review of the literature and expert opinion. A total of 26 experts from 8 countries participated. The top three short-term priorities were to better leverage existing databases for research, to develop and disseminate educational resources on post-sepsis morbidity, and to build deep connections with sepsis survivors to define and achieve research priorities. The top longer-term priorities were to link mechanisms to long-term outcomes through large cohort studies with deep phenotyping, build a harmonized global sepsis registry from which patients could be enrolled into cohort studies or interventional trials, and to complete detailed longitudinal follow-up to characterize the heterogeneity of recovery experiences across sepsis survivors. This Perspective reports on the Colloquium discussions, the rationale for the research priorities, and current initiatives addressing these priorities.

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INTRODUCTION

Sepsis—life-threatening organ dysfunction caused by a dysregulated host response to infection—is a leading cause of global morbidity and mortality. An estimated 14.1 million adults and 2.5 million children survive sepsis each year[1,2], and many survivors experience poor long-term outcomes[3]. Patients develop an average 1-2 new functional limitations following sepsis[4], and 10-40% experience new cognitive impairment[4-7]. Anxiety[8], depression[9], and post-traumatic stress disorder[10] symptoms exceed population-level norms. Furthermore, sepsis survivors are vulnerable to further health problems[3]. Up to 40% are re-hospitalized within 90 days[11], and rates of recurrent infection, sepsis, cardiovascular events, acute renal failure, and aspiration are increased relative to age- and co-morbidity matched controls[3,12-14]. As a result, sepsis survivors are often unable to live independently after sepsis[15], cannot return to work[16], and have increased risk of dying for up to two years[17]. Thus, sepsis should be viewed as a life-changing and disability-inducing event.

A 2017 WHO resolution on sepsis called on member states to address the needs of survivors, recognizing the burden of longer-term sepsis-related morbidity[18]. However, guidelines have traditionally focused on early recognition and management, not mitigation of longer-term sequelae[19]. Likewise, clinical trials typically use shorter-term mortality endpoints and only rarely collect data on functional outcomes or quality of life[20,21]. Perhaps not surprisingly given the lack of attention to sepsis survivorship, many patients report dissatisfaction with follow-up care after hospitalization[22].

To address this unmet need, a Colloquium on “Understanding and Enhancing Sepsis Survivorship” was held in February 2018, sponsored by the International Sepsis Forum. The Colloquium brought together a diverse group of healthcare professionals, researchers, and patient representatives to distill essential findings on sepsis survivorship and articulate how to improve longer-term recovery. This Perspective reports on gaps and limitations of current knowledge on sepsis survivorship; research priorities and their rationale; and current initiatives to address these priorities.

METHODS

The Colloquium chairs (HCP, KMR, DCA) identified participants based on their expertise and through snowball sampling by recommendation. Participants outside critical care and infectious disease were intentionally invited to provide experience and examples of successes in analogous areas. Collectively, the group had expertise in sepsis, critical care, infectious diseases, geriatrics; physical medicine & rehabilitation, psychology, and physiotherapy.

During the Colloquium, we used “nominal group technique” to rapidly gain consensus on research priorities. This process involves problem identification, solution generation, and decision making by group vote[23]. Prior to Colloquium, participant were asked to consider gaps and limitations of current research (based on literature review and their expert opinion), then generate potential next steps to move the field forward. During the Colloquium, ideas were shared through presentations and group discussion (see Online Supplement, **Appendix 1** for Colloquium agenda). At the end of the Colloquium,

participants listed potential next steps over a two-year and ten-year horizon—to "do more with what we have" in the shorter-term and "develop and deliver more" in the longer-term. Ideas were prioritized by group vote. Each participant could cast 12 votes, 6 for shorter-term and 6 for longer-term priorities. Votes could be allocated in any way—all 6 for a single idea or split amongst several ideas. Following the Colloquium, the organizing chairs drafted the manuscript, which was circulated to participants for critical appraisal, revision, and final approval.

RESULTS

Summary of Evidence

Our discussion was informed by recent comprehensive reviews on adult sepsis survivorship[3] and pediatric critical illness survivorship[24]. In addition, participants identified 30 recent systematic reviews pertinent to sepsis survivorship (**Table 1**). The main findings, as well as the gaps and limitations identified by these systematic reviews, are summarized in **Supplemental Table 1.**

Limitations of Existing Research

Participants identified the following limitations of as most important: (1) variable inclusion/exclusion criteria, outcomes measures, and timing of outcome assessments, making it difficult to pool studies to yield larger and more generalizable study populations, and (2) small or non-representative patient populations (**Supplemental Tables 1, 2, Supplemental Figure 1)**.

Gaps in Research

Participants identified the following gaps as most important: (1) limited data on longer-term outcomes of specific patient populations, such as pediatric sepsis survivors and the majority of sepsis survivors who reside in low or middle-income countries; (2) limited data on outcomes beyond one year; (3) few studies of in-hospital or post-hospital interventions to enhance longer-term survival and quality of life; (4) limited data on how to identify patients most likely to benefit from interventions (**Supplemental Tables 1, 3, Supplemental Figure 1**). In particular, more research is needed to define the benefit and optimal delivery of early mobilization; physical rehabilitation; early cognitive rehabilitation; peer-support; supportive interventions for caregivers; and interventions to assist survivors in adapting to new limitations.

Successes in Related Fields

Relevant expert participants presented models of success in the fields of cancer, dementia, stroke, and traumatic brain injury that each have research programs promoting recovery and/or adaptation to new limitations (**Table 2**). Dedicated follow-up clinics, which serve both to support patients and to generate and test research hypotheses, exist for each of these conditions in at least some countries. Additionally, these fields, particularly cancer, have large-scale public awareness campaigns, philanthropy-funded research programs, successful integration of patients into the prioritization of research questions, and large-scale longitudinal registries. These solutions should be adapted and applied to sepsis survivorship.

Is Sepsis Survivorship Unique?

During the Colloquium, we considered the extent to which sepsis survivorship is a unique problem. Many challenges are shared with broader populations of patients surviving an acute illness[25,26]—as described by "post-hospital syndrome"[27] (an acquired, transient period of generalized risk for a range of adverse health events); "post-intensive care syndrome"[28] (new or worsened physical, cognitive, or emotional morbidity after critical illness); and "persistent inflammation, immunosuppression, and catabolism syndrome"[29] (a collection persistent physiologic derangements following sepsis, trauma, or major surgery). Moreover, patients' experiences after sepsis are often influenced by multi-morbidity, frailty, and progressively declining health prior to sepsis[30,31]. For this reason, the magnitude and type of post-sepsis problems measured in studies depends heavily on the comparison—whether sepsis survivors are compared to age- and gender-matched population controls, patients hospitalized for infection, or to other ICU patients.

Despite the overlap with other populations, there are some benefits to focusing research and treatment on sepsis survivors rather than general ICU survivors. Serious sequelae of sepsis are not limited to patients treated in an ICU. Furthermore, organizing educational information around sepsis may be more accessible to patients, who rarely self-identify as ICU survivors. Indeed, a growing number of websites provide information on "life after sepsis"[32,33], "post-sepsis symptoms"[34], or "post-sepsis syndrome"[35,36].

Discussion Themes

The following themes emerged as central foci (**Figure 2**):

- *Promoting education, advocacy, and patient engagement.* Awareness of sepsis sequelae is poor among general public and clinicians outside critical care. Advancing research and treatment of sepsis survivors requires broader awareness—to direct patients to existing resources, define and refine best practices for clinical management, and increase research funding. Finally, there is limited interaction between researchers and patient engagement groups, missing a critically important opportunity.

- *Building clinical infrastructure*. Sepsis survivors are treated by a variety of healthcare providers across diverse clinical settings. Specialized follow-up, such as critical illness follow-up clinics or sepsis centers of excellence, is one possible approach to address the multi-faceted problems faced by sepsis survivors and mitigate secondary disabilities. By concentrating learning-by-doing and providing a setting to pilot and test novel rehabilitation strategies more efficiently, centralized follow-up programs may advance care. For example, the Society of Critical Care Medicine's International Thrive Collaboratives for ICU Peer Support[37] and ICU Follow-up Clinics[38] provide a setting to learn through shared experiences. However, because many sepsis survivors cannot travel to centralized clinics, care models must be expanded beyond traditional in-person clinics, potentially incorporating remote monitoring, telehealth, and in-home visits.

Alternatively, lessons learned from specialized follow-up clinics must be scaled for broader delivery.

- *Improving research methodology*. Better research tools are needed to identify the mechanisms underlying post-sepsis morbidity and identify successful interventions. Particular areas of need include robust and proximal surrogate outcome measures that distinguish underlying mechanism of injury; measures that precisely characterize patient outcomes while minimizing response burden; theory-guided interventions (*i.e.,* tailoring interventions to the mechanism/type of impairment), longer duration of longitudinal follow-up, and translational studies leveraging multi-modal assessment (from gene expression through patient reported outcomes).

Prioritization of Short- and Long-Term Research Goals

The top short-term priorities were: (1) merging ICU databases across countries and developing consensus harmonized data elements for such databases (15.2% of votes); (1) developing and disseminating educational materials for patients, families, and clinicians (15.2%); and (3) making deep connections with survivor groups to define and achieve research priorities (14.5%) (**Figure 2).** Full voting on short-term priorities is presented in **Supplemental Table 5**.

Top long-term priorities were (1) building an integrated global cohort study linking mechanism to long-term outcomes (17.4% of votes); (2) building a global sepsis cohort

to feed into observational and interventional trials (15.9%), and (3) incorporating detailed long-term longitudinal follow up to characterize trajectories of recovery/survivorship across patients (14.5%) (**Figure 2**). Full voting on long-term priorities is presented in **Supplemental Tables 6.**

Shorter-Term Priority 1: Harmonizing and linking existing ICU databases

A number of high-quality ICU databases[39-41], while not primarily developed for research, have proved valuable to answering research questions. Moreover, ICU databases have recently been developed in several lower and middle-income counties[42-44]. However, these databases are rarely linked to each other or to other data sources. As such, research questions are often limited to those that can be answered within the single database, constraining generalizability to select regions or hospital systems, and to the shorter-term outcomes collected.

Investing in data linkages would realize the full potential of existing data, facilitate longer-term follow-up, and enable cross-system comparisons. For example, Brazil's Organizational CHaractEriSTics in cRitical cAre study (ORCHESTRA) database was recently linked to the UK's Intensive Care National Audits & Research Centre (ICNARC) Case Mix Programme database to compare prevalence and outcomes of ICU-treated sepsis between Brazil and England[45].

Importantly, it is not necessary to share patient-level data. Rather, analyses can be completed in secure data enclaves[46] or by pooling aggregate results, as was done for the Sepsis-3 validation[47] and evaluation of US sepsis incidence[48].

Beyond linking existing databases, ICU dataset specifications should be harmonized, such that basic demographic, illness severity, and treatment data are collected in a consistent manner on consistent scales to facilitate comparison.

Shorter-Term Priority 2: Developing and disseminating educational materials.

Public awareness of sepsis has increased in recent years, but recognition still lags behind other acute medical conditions[49], and awareness of long-term sequelae (*e.g.* physical and neuropsychological impairment, increased risk for recurrent infection) remains particularly low. The challenges of sepsis survivorship are not covered in current sepsis guidelines[19] and are rarely discussed during hospitalization[22,50].

Several educational resources on sepsis survivorship have been developed [32,33,36,51,52]. However, these materials must be disseminated more broadly. Panelists recommend: (1) educating patients and families about life after sepsis in the peri-discharge period; (2) developing and disseminating educational materials to clinicians working in post-acute care facilities and the outpatient setting, such as this recent perspective on sepsis survivorship geared towards physical therapists[53]; and (3) incorporating education on sepsis sequelae into medical school curriculum, professional society conferences, and continuing medical education opportunities.

Shorter-Term Priority 3: Building deep connections with survivor groups to define and achieve research priorities.

Patient advocacy groups play an important role in defining research priorities and funding research for many diseases. For example, the Cystic Fibrosis Foundation funds drug development and randomized clinical trials. Their website reports that "nearly every CF drug was made possible by the Foundation and because of funds raised from Great Strides [walks]"[54].

Sepsis advocacy groups—such as Global Sepsis Alliance[55], UK Sepsis Trust[56], Latin American Sepsis Institute[57], Sepsis Alliance[58], and Rory Staunton Foundation[59]—have spurred large-scale awareness and quality improvement initiatives, such as World Sepsis Day[60,61], nationwide quality improvement programs in Brazil[62], and "Rory's Regulations" in New York[63,64]. These efforts have saved lives. Moreover, in 2017, the World Health Organization passed a resolution recognizing sepsis as a global health priority[18].

Despite these successes, patients have historically been absent from defining sepsis research priorities. Going forward, researchers must better engage with sepsis survivors to advance sepsis research. Recent examples of increased public involvement include: (1) collaboration of patients, caregivers, and clinicians to create the James Lind Alliance's top 10 research questions for intensive care[65]; (2) inclusions of multiple public members on the current Surviving Sepsis Campaign Guidelines panel; (3) inclusion of

patient and caregiver representatives on the Delphi panel for developing core outcomes measures for acute respiratory distress syndrome survivors[66,67]; and (4) co-design of critical illness follow-up clinics by patients and clinicians[68,69].

Longer-Term Priorities:

(1) A global cohort study linking mechanism to long-term outcomes;

(2) A global sepsis registry, from which patients could be enrolled into observational and interventional studies;

(3) Detailed long-term longitudinal follow up to characterize the heterogeneity of recovery across sepsis survivors.

We believe the long-term priorities are best tackled jointly through a systematic research program on sepsis survivorship (**Figure 3**). The European Prevention of Alzheimer's Dementia (EPAD) Consortium—a multi-national industry-academia initiative to "create a novel environment for testing numerous interventions targeted at the prevention of Alzheimer's dementia"—could serve as a model[70]. EPAD aims to advance anti-dementia research and treatment by: (1) improving patients' access to existing cohorts and registers; (2) developing a master registry of patients at increased risk of Alzheimer's; (3) establishing a longitudinal cohort study of 6,000 patients; and (4) deploying a proof-of-concept adaptive trial, enrolling patients from the master registry of at-risk patients[71]. In essence, EPAD connects existing registries and serves as a unified entry point into early-phase clinical trials.

Similar infrastructure could dramatically accelerate sepsis research. Akin to EPAD, a sepsis consortium could start as a harmonized international registry, bringing together existing sepsis registries, such as the Mid-German Sepsis Cohort[72]. From the harmonized registry, patients could be screened and invited to join longitudinal cohort studies. Participation in the consortium could provide a venue for education and peer-support, potentially providing immediate benefits to participants and encouraging retention. Over the longer-term, it would improve understanding of post-sepsis sequelae. Ultimately, adaptive platform trials could be incorporated to test putative interventions after sepsis.

The major limitation to a free-standing sepsis consortium, however, is that data on pre-sepsis health status could be collected only retrospectively. To overcome this limitation, the consortium could be embedded within large ongoing cohort studies (*e.g.* UK Biobank[73], Norway's HUNT Study[74], US National Institutes of Health's All of Us Research Program[75], US Department of Veterans Affairs' Million Veterans Program[76]), which already collect genetic and health data on millions of individuals.

Cohort studies (*e.g.* US Health and Retirement Study[77], Cardiovascular Health Study[78]), have already been leveraged to measure the impact of pre-sepsis health status/trajectory on sepsis outcomes[30,79]. However, in these studies, sepsis cases were identified by diagnosis codes in linked claims data, and there is limited data on patient outcomes in the months after sepsis hospitalization.

Prospectively embedding a sepsis consortium within ongoing cohort studies would provide several distinct benefits over existing research, including: (1) accurate identification of sepsis cases by prospectively collecting data on all potential sepsis hospitalizations, (2) better characterization of sepsis, and (3) increased intensively of data collection to characterize recovery after sepsis (*e.g.* serial collection of biospecimens and patient-reported outcomes).

A global, harmonized sepsis consortium would be a natural arena to advance standardized core baseline variables and core outcome sets for sepsis[80]; refine their measurement across the continuum of sepsis; and develop platforms to collect such information across participating sites, drawing directly from electronic health records and existing databases when possible. The consortium could also promote non-mortality outcomes, following the US Federal Drug Administration's "Critical Path" process for proxy outcome development[81], and select from existing (or develop new) IRT-based instruments to measure core outcomes in a way that maximizes information and minimizes participant burden.

Sepsis survivorship research has often focused on a particular outcome (*e.g.* cognitive function, physical function, healthcare utilization) or a particular aspect of the underlying mechanistic pathways driving morbidity and mortality (*e.g.* genomics, transcriptomics, or proteomics in isolation). However, a sepsis consortium could support broad translational studies—simultaneously examining genomic and transcriptomic host response along

with multi-faceted patient outcomes—to understand the mechanisms driving the long-term morbidity and mortality (**Figure 2**).

Finally, while prior cohort studies have defined the average experience of patients in the year after sepsis, there is wide heterogeneity of experiences across individual patients. It is hypothesized that there are characteristic trajectories of recovery, adaptation, and ongoing/progressive disability after sepsis[82]. A sepsis consortium could support large, population-based cohorts with detailed longitudinal follow-up necessary to: (1) objectively identify and define the characteristic pathways of recovery versus disability after sepsis; (2) predict a patient's likely post-sepsis trajectory; (3) identify modifiable factors influencing a patient's recovery experience that could be targeted in future interventional studies (**Figure 3**).

Additional areas of focus

Beyond the top research priorities, there was considerable interest in: (1) developing an item-response theory (IRT) computerized adaptive testing (CAT) question bank for long-term sepsis outcomes, and (2) developing better animal models of sepsis.

Current instruments to assess post-sepsis outcomes (*e.g.* neuropsychological status, quality of life) may not detect subtle declines—but detailed assessments impose expense and respondent burden. CAT characterizes a person's ability more precisely and efficiently than standard surveys, is used widely in other settings (*e.g.* intelligence testing), and was recently used to study functional recovery after pediatric critical

illness[83]. CAT would be useful for characterizing heterogeneous outcomes of sepsis survivors, but questions must first be selected and calibrated for use.

For pre-clinical studies, animal sepsis models reproduce many of the acute immune defects seen in septic patients, but are currently insufficient for studying longer term recovery. In most instances, animals are young, have no co-morbid disease, and are not treated with typical sepsis therapies (*e.g.* antibiotics, fluids, supplemental oxygen). Furthermore, as the goal is often to study short-term survival, animal models have been designed such that only a minority of animals survive the insult. These limitations have been addressed in a recent expert consensus initiative for improving animal modeling in sepsis, which aims to improve the translation of preclinical findings[84].

CONCLUSION

Sepsis is a common cause of hospitalization that frequently results in new morbidity. Shorter-term priorities to improve outcomes for survivors include leveraging existing databases, improving awareness of post-sepsis morbidity, and connecting with sepsis survivors to define and achieve research priorities. Longer-term priorities are to understand the mechanisms driving long-term sequalae and characterize heterogeneity of recovery experiences, both of which will inform future interventions. These longer-term priorities may be best accomplished through a global, harmonized sepsis research consortium embedded within existing large prospective cohorts.

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Table 1: Recent Systematic Reviews Pertinent to Sepsis Survivorship

Topic	Number of Reviews, Total (Sepsis-Specific)	Total Number of Included Studies
Outcomes		
Cognitive	3[85-87] (2[85,87])	168
Emotional	4[8-10,88] (0)	102
Functional	3[89-91] (0)	53
Mortality	2[1,92] (2[1,92])	69
Quality of Life	2[93,94] (1[93])	62
Other	2[95,96] (0)	44
Interventions		
Early Mobility	6[97-102] (1[101])	88
Rehabilitation	3[103-105] (0)	27
Other	4[106-109] (0)	31
Research Methods		
Performance of outcome measures	1[110] (0)	20
Total	**30 (6)**	592

Summaries of the 30 systematic reviews are presented in **Supplemental Table 1**.

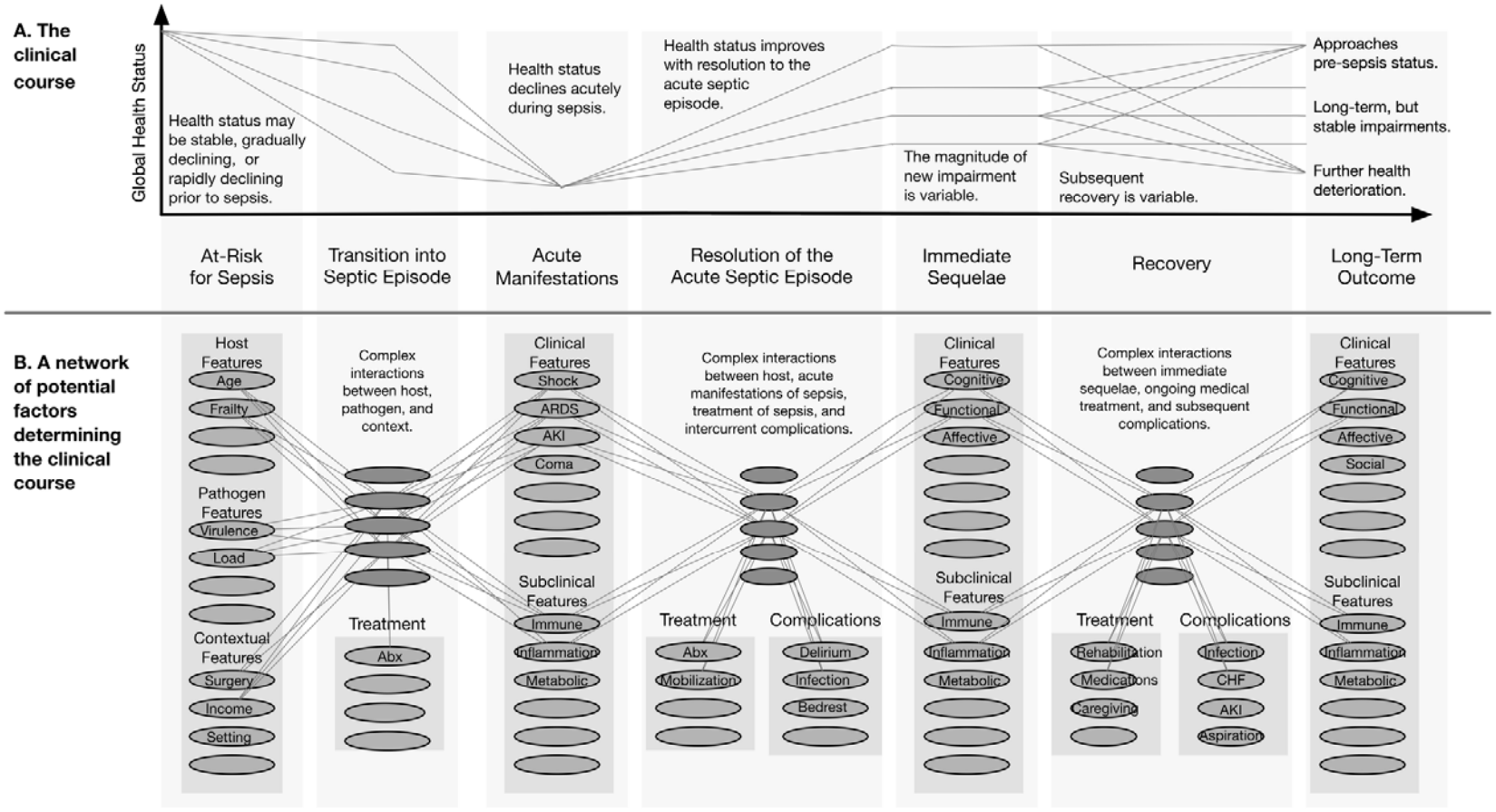
Table 2: Models of success from other fields

Analogous Condition	Similarities	Differences	Successful programs, which may be appied to sepsis
Cancer	Like sepsis, cancer and its treatment commonly result in new morbidity, increased risk for certain medical complications, and post-acute mortality.	The duration of cancer treatment is longer, such that patients are more likely to self-identify as cancer survivors. A defined specialty group provides both the acute and longer-term care.	Large-scale registries, and an International Association of Cancer Registries[59] Registry-RCT linkages Public Awareness Campaigns Philanthropy-funded research Long-term follow-up clinics Peer Support Groups
Dementia	Like sepsis, dementia typically occurs in older patients with multi-morbidity and often requires family members to take on care-giving roles. Like sepsis, dementia has suffered from a lack of targeted therapies entering the market despite improved understanding of its pathophysiology.	Unlike sepsis, many dementias are slowly progressive diseases. A defined specialty group provides both the acute and longer-term care.	Regional registries of dementia patients[60]. Industry-academia research collaboration with multi-national register, standardized follow-up, and intentional invitations to participate in early stage 'adaptive' clinical trials (*e.g.* European Prevention of Alzheimer's Dementia Consortium, EPAD[46,47])
Stroke / Traumatic Brain Injury (TBI)	Like sepsis, stroke and TBI may be followed by profound new functional and cognitive limitations.	More focal injuries with discrete lesions and association functional and cognitive limitations. A defined specialty group provides both the acute and longer-term care.	Structured acute rehabilitation and long-term follow-up programs. Regional registries of TBI patients[61,62].

Figure 1: Shorter and longer-term research priorities by theme

	Shorter Term Priorities	Longer Term Priorities
 Promoting education, advocacy, and patient engagement	• Build deep connections with survivor groups to define and achieve research priorities • Develop and dissemine educational materials for patients and families	• Build a global registry to improve patient access to cohorts and trials
 Building clinical infrastructure	• Disseminate educational materials for clincians • Incorporate post-sepsis sequelae into medical school curriculum and continuing medical education	• Develop specialized follow-up programs —dedicated clinics or sepsis centers of excellence. • Adapt follow-up programs to incorporate remote monitoring, telehealth, and in-home visits.
 Improving research methodology	• Harmonize and link existing ICU databases	• Launch an integrated global cohort study linking mechanism to long-term outcomes • Complete detailed longitudinal follow-up to characterize heterogeneity of recovery across sepsis survivors

Figure 2: Conceptual diagram of patients' clinical course through sepsis and underlying factors that influence an individual patient's trajectory

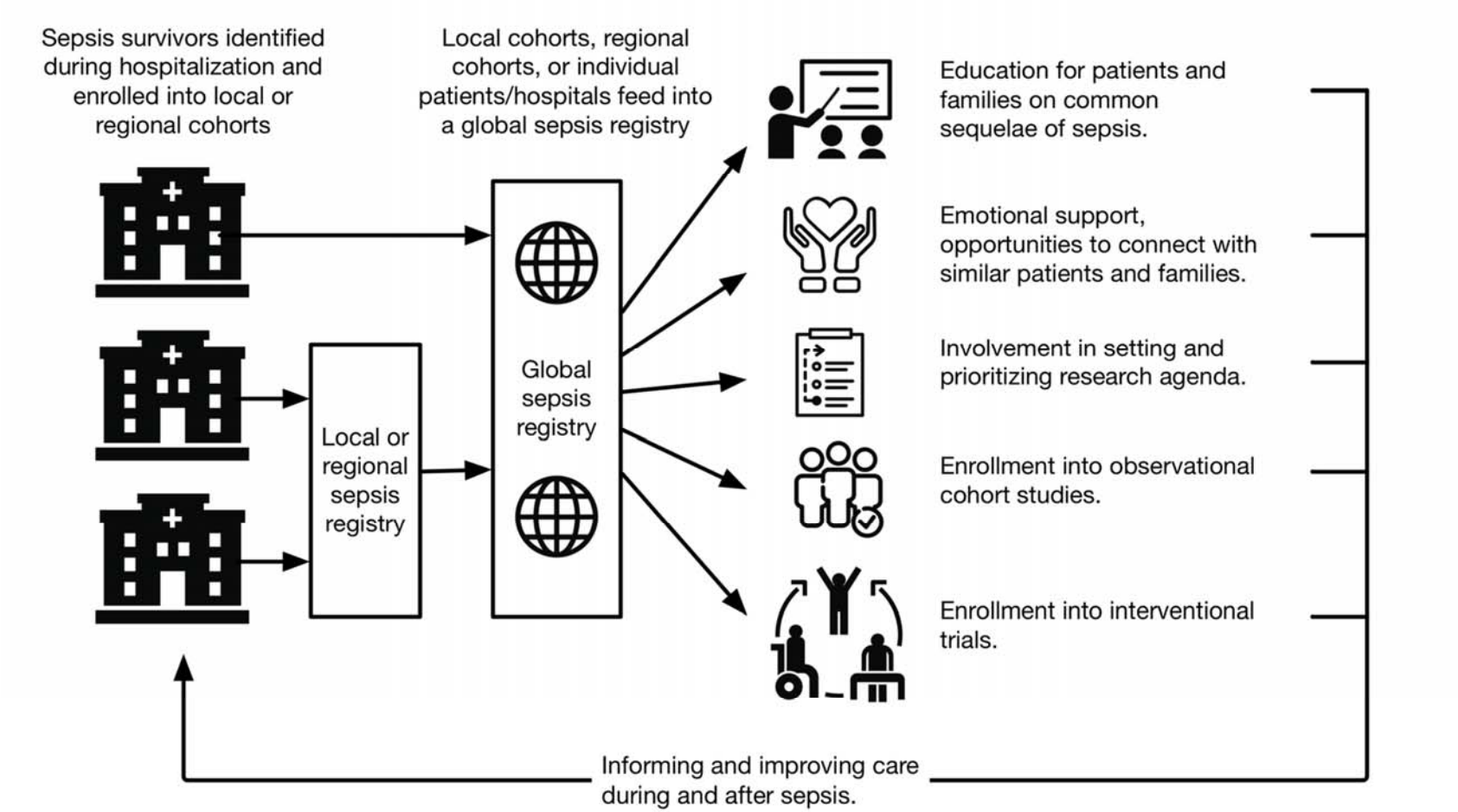


There are many potential clinical courses that a patient may experience after a hospitalization for sepsis, from rapid complete recovery to recurrent complications and death. This figure (adapted from a conceptual diagram first promoted in Prescott and Angus, *JAMA*, 2018[2]) depicts common clinical trajectories (top panel) and presents factors important to shaping a patient's clinical course and long-term outcome (bottom panel). This figure draws from the Wilson-Cleary model[63], which links underlying biologic factors to

physical function and quality of life, but extends the representation of the biologic factors to demonstrate their complex and unmeasurable interactions.

Observable factors, such as presenting features and clinical manifestations of disease, are presented as light-grey ellipses, while the unmeasurable biological interactions are presented as dark-grey ellipses. Not all ellipses are labelled, representing our incomplete knowledge of the factors determining clinical course. This diagram is intended to convey that innumerable factors interact in complex ways to determine a patient's long-term outcome, and that the measurable manifestations of disease cannot fully predict the evolution of a patient's recovery because of the unmeasurable biological interactions at play.

Figure 3: Conceptual diagram of global sepsis registry



While some services (education, emotional support) are ideally provided locally or regionally, they are not universally available. A global sepsis registry could provide universal opportunities for enrollment into cohorts and interventional trials, as well as safety net services for patients without local sepsis survivorship resources.